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Impaired outcome colitis-associated rectal cancer *versus* sporadic cancer

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ABSTRACT

Background: The surgical management of colitis-associated rectal cancer (CARC) is not well defined. This study determines outcomes after surgery for CARC compared with sporadic rectal cancer.

Materials and methods: This is a retrospective cohort study comparing 27 patients with CARC with 54 matched patients with sporadic cancer. Matching criteria included age, gender, neoadjuvant chemoradiation, and American Joint Committee on Cancer stage. Outcome measures were disease-free and overall survival, tumor characteristics, and postoperative morbidity.

Results: Compared to those with sporadic rectal cancer, patients with CARC underwent proctocolectomy more frequently (21 [78%] *versus* 6 [22%] $P < 0.001$) and were more likely to have mucinous tumors (11 [40.7%] *versus* 12 [22.3%] $P = 0.03$). Overall 3-y survival was significantly reduced in CARC patients compared with patients with sporadic rectal cancer. Those with CARC undergoing segmental proctectomy only demonstrated reduced overall and disease-free survival compared to patients with sporadic rectal cancer and to colitis patients undergoing proctocolectomy ($P = 0.002$).

Conclusions: Patients with CARC undergoing proctectomy demonstrate reduced disease-free survival *versus* those undergoing proctocolectomy, and *versus* patients with sporadic rectal cancer undergoing proctectomy. These findings warrant further study and suggest that proctocolectomy should be considered the preferred surgical approach for CARC.

Introduction

Inflammatory bowel disease (IBD) is a well-established risk factor for the subsequent development of colorectal cancer (CRC).[1-3] Those with primary sclerosing cholangitis, a family history of CRC, young onset of IBD, long duration of IBD, and high severity of disease are at particularly increased risk of developing CRC.[4-6] However, improved and targeted screening methods[7] in combination with timely prophylactic surgical resection[8,9] have been shown to reduce the incidence of colitis-associated CRC.[10-12] Despite these preventative measures, however, up to 15% of all IBD-related mortality can be attributed to CRC.[13-15] There is

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conflicting literature on oncologic outcomes after surgery with curative intent in patients with IBD-associated CRC compared with matched groups of patients with sporadic CRC.[16-19] Previous reports suggest that IBD patients present with CRC at an earlier age and with more advanced disease than those with sporadic CRC.[20,21] The literature is limited, however, with respect to colitis-associated rectal cancer (CARC) specifically, which has unique considerations such as surgical approach and use of neoadjuvant therapy. Although total proctocolectomy is generally the procedure of choice for those with ulcerative colitis (UC) and Crohn's disease, segmental resection is used in select cases for those with Crohn's disease.[19] However, the impact of the type of surgical procedure on the oncologic outcome in patients with CARC is not well defined. Accordingly, the primary aim of this study was to compare oncologic outcomes in patients with CARC to a matched (1:2) group of patients undergoing resection for sporadic rectal cancer. Secondary aims include comparing short-term surgical morbidity, surgical approach, and tumor histopathology.

Methods

Patients

This study was conducted as an institutional review board–approved retrospective review (institutional review board ID# 201402017) performed on a prospectively maintained database of patients undergoing colorectal surgery at Washington University School of Medicine in St Louis. The database was queried for patients with IBD undergoing surgery for rectal cancer between 1993 and 2012. Only patients with both diagnoses (IBD and rectal adenocarcinoma) confirmed on final histopathologic evaluation of the surgical specimen were included. These patients were matched 1:2 to patients undergoing resection of sporadic rectal cancer between 2002 and 2009 by the following criteria: age at surgery (±5 y), gender, neoadjuvant chemoradiation, and American Joint Committee on Cancer stage. Patients with a positive test result for a hereditary CRC syndrome on genetic screening, pathology reports unavailable for review, and those lost to follow-up after hospital discharge were excluded from the study. Patient demographics, comorbidities, detailed operative information, histopathologic tumor features, and follow-up data were obtained by medical record review. If required, survival data were supplemented by querying the US Social Security Death Index. The primary outcomes compared were disease-free and overall survival. Recurrent disease was defined as disease that became apparent after a period of undetectable disease including local recurrence in the same location as the primary tumor, regional recurrence, and distant recurrence in other organs such as liver and lungs. Secondary outcomes studied included tumor characteristics and histology, surgical approach (proctectomy *versus* proctocolectomy), and short-term (30 d) surgical outcome.

Surgical procedures

All surgical procedures were performed by board-certified colon and rectal surgeons at a tertiary referral center. Resections for rectal cancer included segmental proctectomy using standard total mesorectal excision technique by low anterior resection or abdominoperineal resection and extended resection by total proctocolectomy. The decision to perform proctectomy or proctocolectomy in CARC patients was made based on an informed discussion between the surgeon and patient, considering the type (UC *versus* Crohn's), extent and severity of colitis, risk of recurrence of cancer and/or colitis, patient characteristics including age, comorbidities, and continence/sphincter function, and expected results of the type of surgery on quality of life. The severity of 30-d postoperative complications was graded using the accordion severity grading system of surgical complications.[22]

Statistical analysis

Categorical variables are expressed as percentages and compared by Fisher's exact test or chi-square test as deemed appropriate. Continuous variables are presented as the mean ± the standard error of the mean or the median and interquartile range (IQR) per group and are compared using two-tailed Student *t*-test. The Kaplan–Meier method was used to generate 1-, 3-, 5-, and 10-y survival curves, and survival was compared by log-rank test. Survival percentages per measured time point are reported with 95% confidence interval (CI). Significance was set at $P < 0.05$. Calculations were performed using IBM SPSS Statistics for Windows, version 20.0 (IBM Corp, Armonk, NY) and GraphPad Prism version 6.03 for Windows (GraphPad Software, La Jolla, CA; www.graphpad.com).

Results

Patient demographics

A total of 36 patients with CARC undergoing surgery were identified from our database, and 27 of 36 (75%) were used for further analysis after applying exclusion criteria. Ten of twenty-seven (37%) patients were diagnosed with UC, and 14 of 27 (52%) were diagnosed with Crohn's disease. In addition, 22 of 27 (81%) had biopsy-confirmed rectal adenocarcinoma before surgery, and the remaining five (9%) underwent surgery for dysplasia in combination with an endoscopically confirmed mass and/or stricture (Table 1). The 27 CARC patients were matched to 54 of 1073 sporadic rectal cancer patients. All matching criteria were met. Median follow-up after surgery for rectal cancer in the CARC group was 2.7 y (IQR 1.3-10.1) and 5.3 y (IQR 4.1-8.0) in the sporadic group.

Overall survival and disease-free survival

Overall survival was not significantly different at 1, 5, and 10 y after surgery, but at 3 y after surgery, CARC patients demonstrated significantly increased mortality when compared with patients with sporadic rectal cancer (Fig. 1A). There was no difference in disease-free survival at 1, 3, 5, and 10 y after surgery between sporadic and CARC patients (Fig. 1B).

Surgical approach, complications, and oncologic outcome

In patients with CARC, significantly more underwent total proctocolectomy as opposed to segmental proctectomy alone

Table 1 – CARC patient demographics.

Variable	(n = 27)	
Type of colitis		
Ulcerative	10	37%
Crohn's	14	52%
Indeterminate	3	11%
Family history of colorectal cancer (y)	7	26%
Primary sclerosing cholangitis (y)	2	7%
Medication before surgery		
Biologics	5	19%
Steroids	12	44%
5-ASA	11	41%
Azathioprine	3	11%
Any colitis-associated medication	20	74%
Age of onset colitis (median, range)	25	12-68
Duration of colitis (median, range), y	20	0-46
Diagnosis before surgery		
Biopsy-confirmed adenocarcinoma	22	81%
Dysplasia, mass/stricture	5	19%

ASA = American Society of Anesthesiologists.

(21 [78%] *versus* 6 [22%], respectively, $P < 0.001$). Of note, among those with CARC undergoing proctectomy alone, 83% had Crohn's colitis, and all had biopsy-confirmed adenocarcinoma before surgery. In addition, total lymph node yield was higher among those with CARC (23 ± 4 *versus* 11 ± 1, $P = 0.01$), and the distal margin was greater (5 ± 0.8 cm *versus* 3 ± 0.3 cm, $P = 0.02$) when compared with the sporadic group, which is expected due to the increased proportion of CARC patients undergoing proctocolectomy. Interestingly, despite the increased proportion of patients undergoing proctocolectomy in the CARC group, no differences were observed between groups regarding the incidence and severity of postoperative complications, length of stay in hospital, and readmission rates (Table 2). When comparing overall survival in sporadic and CARC patients who underwent segmental proctectomy alone, we found trend toward increased mortality in CARC patients at 3 y after surgery (Fig. 1C). In addition, among those who underwent segmental proctectomy alone, disease-free survival at 3 y was significantly lower in CARC compared with sporadic rectal cancer patients (Fig. 1D). Given these findings of reduced overall and disease-free survival in CARC patients undergoing proctectomy, we next compared the impact of surgical approach (segmental proctectomy *versus* extended proctocolectomy) on survival in patients with CARC only. Although overall survival was not significantly different at any of the measured time points, disease-free survival in CARC patients undergoing proctectomy was significantly reduced compared with CARC patients undergoing proctocolectomy at 3, 5, and 10 y (Fig. 2B). All cases of recurrent disease in CARC patients occurred within 2 y after surgery and only in those who underwent proctectomy. Other factors that may

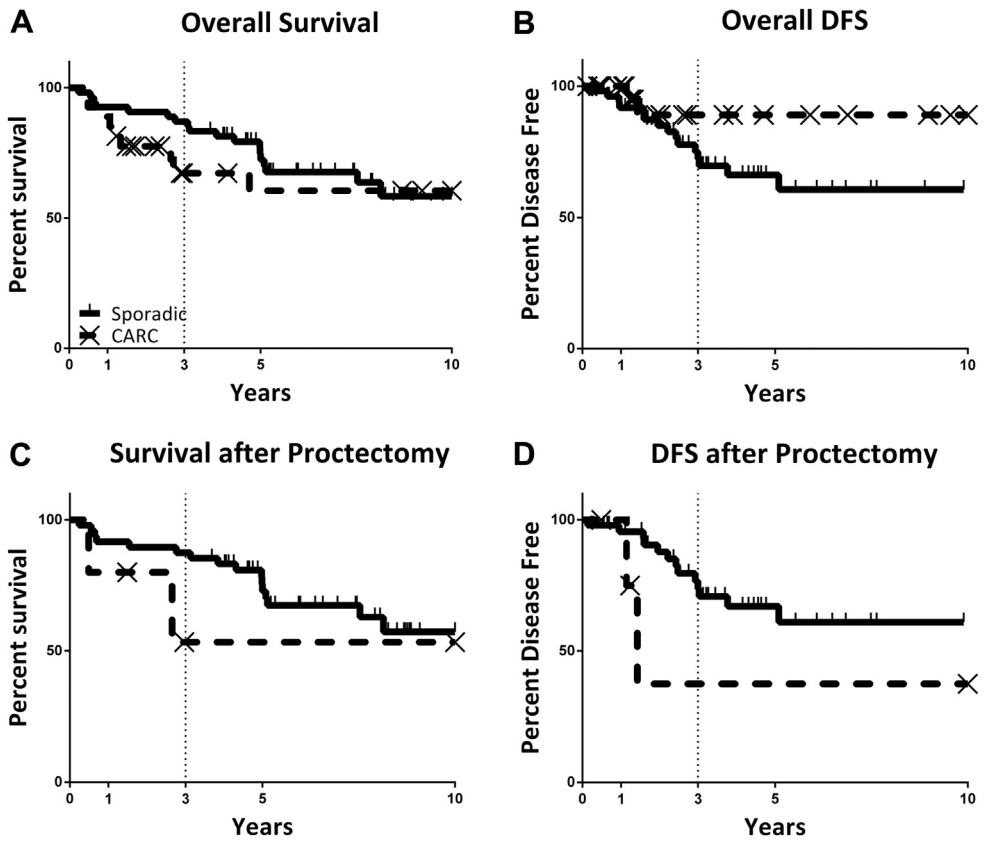

Fig. 1 – Kaplan–Meier survival curves comparing patients with CARC to those with sporadic rectal cancer. (A) Presents overall survival, and (B) presents disease-free survival. In (C) and (D), only those who underwent proctectomy are compared. Three-year survival (A; $P = 0.04$) and disease-free survival (D; $P = 0.051$) were worse in those with CARC.

Table 2 – Univariate analysis of matching criteria and tumor characteristics.

Variable	Sporadic ($n = 54$)		CARC ($n = 27$)		P
Age (mean ± standard error of the mean [SEM])	55	±2	54	±2	0.69
Gender (male)	41	76%	21	78%	1
Neoadjuvant chemoradiation (y)	37	69%	18	67%	1
American Joint Committee on Cancer stage					
I	14	26%	7	26%	
II	14	26%	7	26%	
III	16	30%	8	30%	
IV	10	19%	5	19%	1
Second primary (y)	1	2%	2	7%	0.26
Lymphovascular invasion (y)	14	33%	5	29%	1
Tumor cell composition					
Not defined	1	2%	2	7%	
Nonmucinous	40	74%	13	48%	
Mucinous cells < 50%	11	20%	6	22%	
Mucinous cells > 50%	1	2%	5	19%	
Signet cells	1	2%	1	4%	**0.04**
Differentiation					
Well	5	9%	5	19%	
Moderate	38	70%	13	48%	
Poor	11	21%	9	33%	0.27
Tumor size (cm, mean ± SEM)	3.4	±0.3	3.1	±0.5	0.55

Bold values indicate $P < 0.05$.

Table 3 – Univariate analysis of operative variables and complications.

Variable	Sporadic ($n = 54$)		CARC ($n = 27$)		P
Surgical approach					
Proctectomy	51	94%	6	22%	
Total proctocolectomy	3	6%	21	78%	**< 0.001**
Laparoscopic (yes)	22	41%	10	37%	0.81
ASA score					
2	35	65%	10	37%	
3	19	35%	17	63%	0.06
Charlson comorbidity index	4.4	±0.3	4.5	±0.4	0.94
Body mass index (median, range)	27	16-53	25	15-36	0.07
Total lymph node	11	±1	23	±4	**0.01**
Positive lymph nodes	1	±0.2	2	±0.7	0.31
Radial margin (cm)	0.9	±0.1	0.5	±0.1	0.14
Distal margin (cm)	3	±0.3	5	±0.8	**0.02**
Adjuvant therapy (y)	35	65%	15	56%	0.47
Complication rate	24	44%	14	52%	0.47
Complications per patient (mean ± standard error of the mean [SEM])	0.9	±0.2	1.1	±0.3	0.54
Accordion severity grade (mean ± SEM)	2	±0.2	2	±0.2	0.91
Length of stay in hospital (d, mean ± SEM)	9	±1	9	±1	0.60
Readmission rate	9	17%	7	26%	0.37

ASA = American Society of Anesthesiologists.
Bold values indicate $P < 0.05$.

have been causal to the reduced disease-free survival observed in CARC patients undergoing proctectomy only compared with those undergoing proctocolectomy are summarized in Table 3. On univariate analysis, we were unable to demonstrate any additional causal factors that might readily explain the higher recurrence rate in CARC patients undergoing segmental proctectomy. Of note, the two patients with recurrent disease both underwent neoadjuvant chemoradiation, and both had distant recurrence to the lung.

Tumor histology

Patients with CARC were nearly twice as likely to have mucinous tumors (11 [40.7%] *versus* 12 [22.3%], $P = 0.03$) than sporadic rectal cancer patients. In addition, tumors consisting of more than 50% mucinous cells were mostly associated with Crohn's colitis (80%). No additional differences were observed in tumor characteristics and histology (Table 4). These results

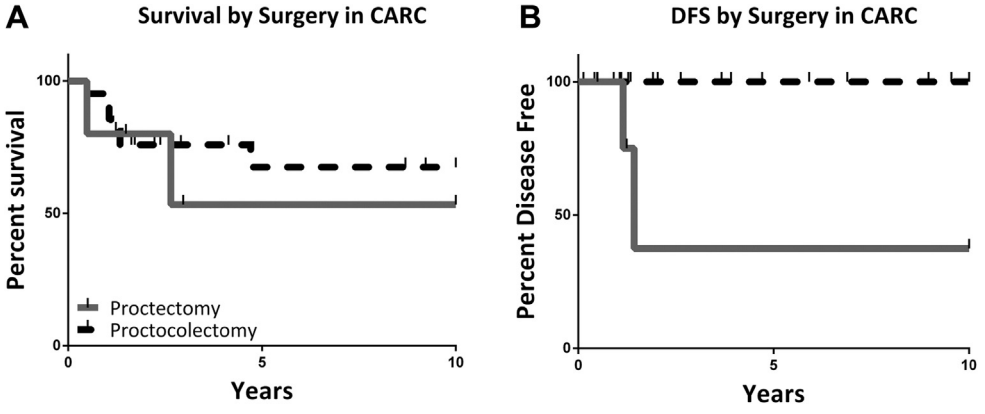

Fig. 2 – Kaplan–Meier survival curves comparing patients with CARC who underwent proctectomy with those with CARC who underwent total proctocolectomy. (A) Presents overall survival, and (B) presents disease-free survival. Disease-free survival was significantly worse in those who underwent proctectomy (B; $P = 0.002$).

Table 4 — Proctectomy *versus* proctocolectomy in CARC patients.

Variable	Proctocolectomy ($n = 21$)		Proctectomy ($n = 6$)		P
Recurrence	0	—	2	33%	0.04
Age (mean ± standard error of the mean [SEM])	56	±3	51	±4	0.40
Gender (male)	14	67%	3	50%	0.58
Neoadjuvant chemoradiation (y)	11	52%	5	83%	0.27
American Joint Committee on Cancer stage					
I and II	12	57%	3	50%	
III and IV	9	43%	3	50%	0.64
T-stage					
1 and 2	7	33%	3	50%	
3 and 4	14	67%	3	50%	1
Positive lymph node(s) (y)	8	38%	2	33%	1
M-stage (1)	2	10%	2	33%	0.19
Lymphovascular invasion (y)	4	19%	4	67%	0.20
Mucinous cell type (y)	9	43%	3	50%	1
Poor differentiation (y)	7	33%	3	50%	0.59
Tumor size (cm, mean ± SEM)	3.1	±0.8	2.9	±0.6	0.91
Radial margin (cm)	0.4	±0.2	0.9	±0.2	0.10
Distal margin (cm)	5.4	±1.1	2.7	±0.2	0.25
Preoperative diagnosis adenocarcinoma (y)	15	71%	5	83%	1
Age of onset colitis (median, range)	27	17-68	25	19-44	0.57
Duration of colitis (median years, range)	20	0-44	24	9-30	0.93

suggest that patients with CARC have tumors with adverse histologic features and thus perhaps biologically more aggressive tumors more commonly than sporadic rectal cancer patients.

Discussion

Long-standing and severe colitis is associated with an increased risk of developing CRC.[4-6] Although the incidence of colitis-associated cancer is low due to improved screening methods in combination with timely prophylactic surgical resection of the colon, up to 15% of colitis-associated mortality can be related to CRC.[13-15] Tailoring surgical treatment of colitis-associated cancer patients may further reduce mortality and the risk of recurrence in this subset of patients. This retrospective, single-center case-matched cohort study of CARC patients puts into perspective the oncologic outcome of rectal cancer in a colitis-associated setting compared with sporadic rectal cancer controls. The key finding of this study is that overall survival is reduced in CARC patients when compared with sporadic rectal cancer patients. Moreover, CARC patients undergoing segmental proctectomy alone demonstrated to have reduced overall and disease-free survival when compared with patients with sporadic rectal cancer patients after proctectomy and CARC patients undergoing proctocolectomy respectively. In addition, mucinous adenocarcinoma was found more frequently in association with CARC compared with sporadic rectal cancer. These findings overall suggest that CARC has a more aggressive biologic phenotype than sporadic rectal cancer and support extended proctocolectomy to be the preferred surgical management in patients with CARC. Several aspects of our findings merit further discussion.

Key information obtained by previous studies place our findings into context. A population-based study by Jensen *et al.*[16] compared 279 patients with UC and CRC to 71,259 patients with non-UC CRC between 1977 and 1999 by cross-referencing data from two nationwide Danish databases. These data revealed that those with UC and CRC present at a younger age, but with similar stage distribution compared with those with non-UC CRC. When mortality rates were adjusted for disease status, gender, age at CRC diagnosis, cancer stage, and year of cancer diagnosis, those with UC and CRC had higher mortality rates at 1 y (odds ratio 1.24, 95% CI 1.02-1.51) and 5 y (odds ratio 1.17, 95% CI 1.01-1.36) of follow-up, similar to the findings at 3 y in our study. In a retrospective single tertiary center case-matched cohort study by Delaunoit *et al.*,[17] 290 patients with IBD-associated CRC between 1976 and 1996 (241 with UC and 49 with Crohn's disease) were compared to an equal number of age-, gender-, and TNM classification of malignant tumors (TNM) stage—matched sporadic CRC patients. The rectum was the predominant cancer location in both groups (30% and 44%, respectively). Overall, with a median follow-up of 5 y in both groups, there was no significant 5-y survival difference between those with UC and Crohn's associated CRC and no difference in survival between those with colitis-associated CRC and those with sporadic CRC. However, higher tumor grades ($P < 0.001$) and mucinous differentiation were more

frequent among those with colitis-associated CRC. On secondary, more stratified analysis in the same study, mucinous differentiation was associated with poorer outcome among those with Crohn's disease ($P = 0.003$). Kiran *et al.*[18] primarily compared a group of 176 patients with UC complicated by CRC to a group of 64 patients with Crohn's disease complicated by CRC between 1980 and 2007. The investigators compared local and overall disease-free survival and overall survival of those with colitis-associated CRC to a matched (1:2, by age, gender, tumor site, tumor stage, chemoradiation, and year of surgery) group of patients with sporadic CRC. With median follow-up periods of almost 7 y in each group, none of the oncologic survival curves were significantly different. In another matched-pair analysis by Renz *et al.*,[19] 33 colitis-associated CRC patients who underwent resection between 1991 and 2007 were matched (1:5, by age, gender, tumor stage, tumor site, and date of surgery) to 165 patients with sporadic CRC. About 31% of all patients in this study had rectal cancer. Colitis-associated CRC was associated with higher preoperative cancer antigen 19-9 levels, more preoperative tumor-related symptoms, and higher tumor grades. Direct postoperative morbidity and reoperation after hospital discharge were found to be significantly more prevalent among colitis-associated CRC patients. In addition, after a median follow-up of 4.3 y, the colitis-associated CRC group showed a significantly higher local tumor recurrence rate when compared with those with sporadic cancer (30% *versus* 11%), and accordingly overall (tumor-specific) survival and recurrence-free survival were significantly reduced in those with colitis-associated CRC. On multivariate regression analysis, IBD was identified as a significant independent risk factor associated with increased 5-y mortality. Other significant risk factors identified by this analysis included tumor stage and liver metastasis at the time of surgery.

These results are consistent with our findings and suggest that there are subsets of patients among those with IBD complicated by CRC that demonstrate worse outcome when compared to those with sporadic CRC. Our study is unique to these studies because of its sole focus on rectal cancer, which has considerations of neoadjuvant therapy and surgical approach that are not present in the management of colon cancer. Similar to the study by Delaunoit *et al.*,[17] our study shows that mucinous cell differentiation is more common among those with CARC. In addition, we demonstrate here that patients with CARC show increased mortality after 3 y of follow-up and that those with CARC undergoing proctectomy show reduced disease-free survival compared with those with sporadic rectal cancer and with CARC patients undergoing proctocolectomy. CARC was not associated with increased postoperative morbidity, despite the more extensive surgical procedures performed in this group. Another interesting question raised by our findings is whether there is a biologic difference between rectal cancer associated with Crohn's disease *versus* UC. Our findings suggest that CARC patients who undergo segmental proctectomy alone have reduced overall and disease-free survival compared with sporadic rectal cancer and with CARC patients undergoing proctocolectomy. Because most CARC patients undergoing segmental proctectomy carried a diagnosis of Crohn's disease, this raises the question as to whether rectal cancer in Crohn's disease carries a worse prognosis than rectal cancer in UC and whether this is related to transmural *versus* mucosal involvement of the colonic inflammation. Because of the small numbers of patients in each group, however, this study is unable to answer this question, but, this certainly provides avenues for further investigation.

There are certain limitations of our study that deserve comment. The data for this study were partially recorded retrospectively. Although most of the variables of interest were well documented in electronic medical records, there was not much information available on preoperative and postoperative endoscopic surveillance data and information on the extent and severity of colitis before the diagnosis of rectal cancer. A large portion of this surveillance data and characterization of colitis were obtained at outside institutions and were not available for review. However, all patients had active colitis in their surgical specimen. In 81% of all CARC cases, the indication for surgery was biopsy-confirmed rectal cancer, and in 19%, there was dysplasia, a mass or stricturing disease suggesting that none of the rectal cancers in this cohort were incidental findings in a background of fulminant colitis. In addition, we recommended all patients to adhere to our routine follow-up schedule after surgery for rectal cancer, which follows National Comprehensive Cancer Network guideline recommendations. The median follow-up time of 2.7 y in the CARC group may underestimate mortality and recurrence projections beyond 3 y of follow-up. This is likely true for our cohort because most survival trends and significant findings became evident around the 3-y mark and lost significance at later analyzed time points. Furthermore, the small number of patients in several subcategories did not allow for meaningful multivariate regression analysis to measure the independent effect of variables on oncologic outcome. Instead, we matched CARC patients to sporadic CRC patients by age, gender, whether they had neoadjuvant chemoradiation, and American Joint Committee on Cancer stage and offered a broad range of results from univariate analyses to put significant findings into perspective.

Conclusions

Our study demonstrates that CARC patients have reduced overall survival when compared with sporadic rectal cancer patients undergoing curative resection. In subanalysis, CARC patients undergoing segmental proctectomy only had reduced survival compared with sporadic rectal cancer patients undergoing proctectomy and with CARC patients undergoing proctocolectomy, highlighting the impact of surgical approach to CARC on prognosis. These data suggest that CARC is biologically more virulent than sporadic rectal cancer and that total proctocolectomy should be the preferred surgical approach for the treatment of patients with colitis-associated rectal cancer.

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Authors' contributions: C.K., B.S., and S.D. contributed to study conception and design; and data acquisition, analysis

and interpretation of the text. C.K. and S.D. contributed to drafting of the article. B.S., P.E.W., S.R.H., M.G.M., E.H.B., and J.W.F. contributed to article critical revisions and approval.

Disclosure

The authors report no proprietary or commercial interest in any product mentioned or concept discussed in this article.

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